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Stanley J. Goldsmith, M.D. is the Director of the Division of Nuclear Medicine, Department of Radiology at The New York Presbyterian Hospital and Professor of Radiology and Medicine at the Weill Medical College of Cornell University.

Dr. Goldsmith has recently completed a 5 year term as the Editor-in Chief of the Journal of Nuclear Medicine, the official publication of the Society of Nuclear Medicine. In 1985-86, he served as President of that Society. He is a Life Member and Diplomate of the American Board of Nuclear Medicine, a Diplomate of the American Board of Internal Medicine, and of the subspecialty Board of Endocrinology and Metabolism.

He is a Fellow of the American College of Nuclear Physicians, the American College of Physicians, the American College of Cardiology and a member of the Endocrine Society and the Radiologic Society of North America.

From 1987 to 1995, he was a Commissioner on the New York State Low Level Radioactive Waste Siting Commission. He has served as a consultant to the Food and Drug Administration and the Nuclear Regulatory Commission on issues dealing with the medical uses of radioactive material.

Dr. Goldsmith is the author of approximately 100 scientific and 15 book chapters. Dr. Goldsmith received his undergraduate training at Columbia University and his medical degree from the State University of New York Downstate Medical Center. Thereafter, he trained in Internal Medicine at the State University-Kings County Hospital Center, in Endocrinology and Metabolism at the Mount Sinai Hospital in New York and in Radioimmunoassay and Radioisotope techniques with Dr. Roslyn Yalow and the late Dr. Solomon Berson at the Bronx Veterans Administration Hospital. From 1969-73, he had been the Director of Nuclear Medicine at the Nassau County Medical Center; from 1973-1992, the Director of the Department of Physics-Nuclear Medicine at the Mount Sinai Medical Center in New York; and from 1992-95, he was Clinical Director of the Nuclear Medicine Service, Attending Radiologist and Member at the Memorial Sloan-Kettering Cancer Center in New York and Professor of Radiology at the Cornell University Medical College.

Radioisotopic Treatment of Prostate Cancer

Stanley J. Goldsmith, M.D., Shankar Vallabhajosula, Ph.D., Peter Smith-Jones, Ph.D., Lale Kostakoglu, M.D. and Neil Bander, M.D.

Prostate Specific Membrane Antigen (PSMA) is a well characterized integral membrane glycoprotein, expressed by a very high proportion of prostate cancers. A monoclonal antibody [MAb], J581, has been developed that is specific to the extracellular domain of PSMA on viable prostate cancer cells. We have performed pre-clinical and preliminary clinical studies that indicate significant potential for this antibody as a radionuclide therapy agent.

J591 was radiolabeled with I-131 using iodogen to a specific activity of 400 MBq/mg. Iodinated intact IgG was compared also to Fab'2 and Fab fragments. Immunoreactivity was determined by ELISA and Lindmo methods. Nude mice bearing LNCaP tumors were injected with 20-50 KBq of radiolabeled antibodies. Tumor uptake and biodistribution was studied over a period of 6 days.

Tumor/blood (T/B) ratios with intact J591 were 1.9-2.1 and remained stable over the 6 day period. Radioiodinated F(ab)₂ and Fab fragments showed higher T/B ratios, 2.5-3.6, compared to intact IgG at 2 days post injection, but a significant reduction in the tumor uptake (%ID/g): IgG, 11.7±2.4% vs. F(ab)₂, 4.9±1.3 and Fab, 1.7±0.5. On day 4, J591 tumor uptake was

13.9±4.5 (%ID/g). Over a period of 6 days, the (T/B) and tumor/muscle (T/M) ratios remained fairly constant at 2 and 20 respectively.

A Phase I/II dose escalation study with J591 (0.5-300 mg) and trace ¹³¹I-J591 has been performed in five hormone refractory patients with raising prostate specific antigen (PSA) and CT/MR documented metastatic prostate cancer.

These patients received 0.2-0.4GBq of ¹³¹I-J591 (0.5-1.0 mg). Serial blood samples and 7-day urine samples were obtained. Whole body images on day 0, 1, 3 and 6 were acquired with a dual head camera. 2/5 patients with either soft tissue tumor mass or bone metastases showed tumor uptake of radiotracer. In these 2 patients, the clearance of activity from tumor ($T_{1/2}$ = 106-144 hr) was significantly slower than from liver ($T_{1/2}$ =32-36hr). Based on imaging studies and mono-exponential analysis of data, the whole body clearance was estimated to be $T_{1/2}$ =92±3 hr. The blood clearance, however had a bi-exponential response; a =40±8%, $T_{1/2}$ =0.74±0.4 hr; b =60±8%, $T_{1/2}$ =70±13 hr. Urinary excretion was 7% at 24 hr, 36% at 48 hr and 63% by 6 days.

In 2 of the 3 patients in whom tumor uptake was not identifiable on scan, there was more rapid blood clearance than in the 2 patients in whom tumor was visualized. A higher molecular weight (300-400 KD) radioactive species was identified on HPLC analysis of serum that raises concern about polymerization or spontaneous HAMA in these patients.

These results demonstrate that radiolabeled Mab fragments may have clinical utility as imaging agents where as therapeutic delivery of radionuclide may be better achieved using intact IgG. PSMA targeted radiotherapy of prostate cancer with J591 Mab has significant potential.